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Skin Ulcers and Cocaine Abuse

Adulteration with Levamisole Can Cause Serious Skin Lesions

By Pavel Kopach, MD, and Barbarajean Magnani, PhD, MD

Cocaine use is a well-known public health issue. The United Nations Office on Drugs and Crime estimated that 17 million people worldwide used cocaine in 2015 (1). It estimated that in 2013 the prevalence of cocaine use in the U.S. was 1.6% of the population aged 12 and older. That number has remained stable over the past few years, although it is significantly lower than in 2006 (1).

Street drugs can be altered through many processes, such as substitution, dilution, contamination, and adulteration. Adulteration consists of adding a pharmacologically active or inactive substance to decrease the purity of the drug without making the user aware. Cutting agents are often used to bulk up the weight of an illicit drug.

Levamisole has been a known adulterant of cocaine since at least 2002 (2). A synthetic imidazothiazole derivative, levamisole is a registered pharmaceutical that was first used as an anthelminthic in human and veterinary medicine. It is currently available under the trade name Ergamisol in the U.S., Canada, and South America for use in veterinary medicine. It was briefly used in the treatment of colon cancer, but that use was ended because of reports of it causing agranulocytosis.

In 2009, the U.S. Drug Enforcement Administration estimated that 69% of seized cocaine was contaminated with levamisole. By 2011, that figure had increased to 82% (3). The first case series of agranulocytosis attributed to cocaine adulterated with levamisole was published in 2009. Since then, many other reports of levamisole-contaminated cocaine complications have been published.

Thus, the use of levamisole as a cocaine adulterant represents a legitimate public health issue. This article presents one such case.

Case Presentation

A 47-year-old African-American male presented to the hospital with painful dark skin lesions and ulcerations over his lower extremities as well as oral mucosal ulcers.

The patient's medical history was remarkable for cocaine abuse; chronic hepatitis C virus infection (genotype 1a), for which he never received treatment; and type 2 diabetes with long-term insulin use. The patient admitted to tobacco use, but denied using alcohol or heroin. He admitted to daily cocaine use, but did not know the time of his last dose.

He had presented with similar ulcerative skin lesions one year prior to this admission. An immunologic work-up at that time demonstrated an elevated cryoglobulin concentration of 0.15 mg/mL (reference range: 0.0–0.10mg/mL), a mixed antinuclear antibodies (ANA) speckled/homogenous pattern at a titer of 1:640 (negative <40), an anti-ds DNA value of 77.6 EU (0.0–25.0 EU), and a perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) value of 1:1280 (negative <20). Antibodies to myeloperoxidase were also positive at 34.8 U (0.0–20 U). Pyoderma gangrenosum was clinically suspected, but was ruled out on skin biopsy. Tissue culture revealed *Pseudomonas*, and the patient was treated with antibiotics and discharged.

In his recent admission, the patient presented to the emergency department with a temperature of 37.3 °C, blood pressure of 142/78 mm Hg, heart rate of 81/minute, and respiration rate of 16/minute. A physical exam revealed that both legs had numerous skin lesions of varying sizes, with granulation tissue

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in the wound and no frank evidence of bacterial infection. Scars from previous lesions on his legs and hands were also noted. The sores began as pinhead-sized lesions, eventually blossoming into open, necrotic wounds 1–2 cm in size. He had at least a half dozen on his legs and groin, including his scrotum. The rest of the physical exam was unremarkable.

Laboratory Findings

Upon admission, laboratory findings included a white blood cell count of 5.5 K/µL (4.0–11.0 K/µL), a hemoglobin concentration of 17.5 g/dL (13.5–16 g/dL), and a platelet count of 212 K/µL (150–400 K/µL). His basic metabolic profile was within normal limits. His urine drug immunoassay screen was positive for cocaine, opiates, and oxycodone.

The consultation toxicology service was asked to review the case in light of the positive immunoassay results for opiates and oxycodone. Confirmatory testing by liquid chromatography-tandem mass spectrometry (LC-MS/MS) identified morphine (3400 ng/mL), oxycodone (1300 ng/mL), oxymorphone (160 ng/mL), and noroxycodone (930 ng/mL). No other common opiates were detected (codeine, hydrocodone, hydromorphone, or norhydrocodone).

These results were consistent with the patient receiving morphine and oxycodone at the time of admission, which had not been disclosed at the time of the testing.

Given the patient's presentation, history of cocaine use, and hepatitis C, the differential diagnosis of systemic vasculitis or levamisole-induced vasculitis was considered. Additional LC-MS/MS testing of the patient's urine for levamisole revealed its presence at a concentration of 1.1 mcg/mL (reporting limit, 0.10 mcg/mL).

Biopsy Results

Tissue from a thigh wound was positive for *Staphylococcus aureus.* A biopsy of one of the patient's skin lesions revealed an ulcerated epidermis with pandermal neutrophilic infiltrate. However, there were no signs of small vessel thrombosis or vasculitis (Figure 1).

Based on the clinical presentation as well as the laboratory and pathological findings, the patient was suspected to have either levamisole-induced necrosis or pyoderma gangrenosum, as evidenced by the skin ulceration and microabscesses on the lower extremities.

The patient received appropriate treatment including antibiotics and pain control. He was discharged to home at his request with services, wound care instructions, and close outpatient follow-up.

Discussion

The patient's skin ulceration and microabscess formation on the lower extremities are consistent with levamisole necrosis.

Levamisole was originally used to treat worm infestations in both humans and animals. After it was found to have immunomodulatory properties, it was used to treat inflammatory conditions, such as rheumatoid arthritis and nephrotic syndrome. It was used as an adjuvant to 5-fluorouracil (5-FU) in the treatment of colon cancer. However, because of reports of agranulocytosis, levamisole was withdrawn for human use from the U.S. and Canadian markets in 2000 and 2003, respectively, although it remains available for veterinary use.

Outside of the U.S., it has been used to treat rheumatoid arthritis (4) as well as chronic hepatitis B, HIV, ulcerative colitis, nephritic syndrome, amyotrophic lateral sclerosis, malignant melanoma, breast cancer, and acute myeloid leukemia, with inconclusive results.

Levamisole exerts its immunomodulator and immunoenhancer properties by increasing macrophage chemotaxis and T-cell lymphocyte function (5). It also upregulates Toll-like receptors, stimulates neutrophil chemotaxis, and enhances dendritic cell maturation (6).

Physiological Effects

As previously noted, the adulteration of cocaine with levamisole has been known since 2002 and has been increasing (3). Levamisole is added at approximately 6% by weight with the possible intent to enhance the effects of cocaine. However, the physiological effects of using it in combination with cocaine are unclear. When it was used as an antihelminthic agent, some clinicians noted its mood enhancing and potential antidepressant activity (7). One possibility is that it stimulates nicotinic receptors,

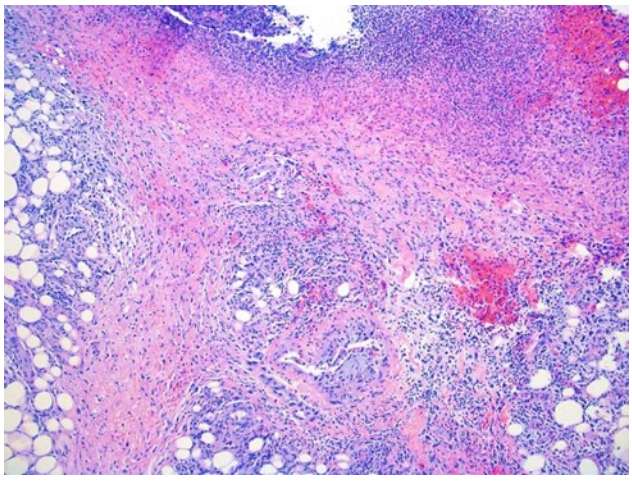

Figure 1. Skin lesion biopsy shows marked pandermal acute inflammation

thus potentiating the nicotinic acetylcholinergic effects of the central nervous system (8).

Cocaine increases sympathetic activity by blocking reuptake of norepinephrine at the postganglionic synapse. Additive effects could be expected when the drugs are combined. Yet, studies of the metabolism of levamisole and its stimulatory effects have shown that levamisole is 100- and 300-fold less potent than cocaine in blocking norepinephrine and dopamine uptake, and has very low affinity for the serotonin transporter. In addition, levamisole does not trigger any appreciable substrate efflux (9).

Levamisole is metabolized to aminorex (9). Aminorex and related compounds, specifically 4-methylaminorex (or "ice"), have high abuse potential because of their amphetamine-like pharmacological activity. Given that the half-lives of levamisole and aminorex exceed that of cocaine, it has been suggested that after the cocaine effect fades out, the levamisole and aminorex effects kick in, continuing the high. (9)

Agranulocytosis and Vasculitis Effects

Significant adverse effects of levamisole include severe agranulocytosis, vasculitis, leukoencephalopathy, and seizures (1). Vasculitis secondary to levamisole treatment was first reported in 1978 and mostly exhibits as leukocytoclastic vasculitis, cutaneous necrotizing vasculitis, and thrombotic vasculopathy without vasculitis.

Levamisole-induced vasculitis is a diagnosis of exclusion. It should be considered in any patient with a history of cocaine use presenting with skin purpura, arthralgia, neutropenia, and high-titer ANCA positivity. Table 1 summarizes the clinical and laboratory findings associated with cocaine levamisole toxicity (12).

Our patient presented with necrotizing skin ulcers on his legs and groin that started as pinhead-sized lesions, eventually blossoming into open, necrotic wounds 1–2 cm in size. However, the patient's complete blood count did not reveal the presence of agranulocytosis and showed only mildly elevated numbers of red blood cells and an increased hemoglobin and hematocrit. These abnormalities corrected within 24 hours after admission and were probably related to dehydration.

Table 1. Clinical and Laboratory Findings in Cocaine-Associated Levamisole Toxicity (12)

Fatigue, joint pain, generalized malaise
Renal failure (pauci-immune focal necrotizing crescentric glomerulonephritis), seizures, pulmonary hemorrhage
Skin necrosis (particularly ear helixes, cheeks, and nose), vasculitis, bullae, retiform purpura
Positive ANA (speckled-pattern), ANCA, dsDNA
Urine positive for cocaine, levamisole

Immunologic studies from the previous admission revealed the presence of cryoglobulins, ANA, anti-dsDNA, and pANCA antibodies, which could have been related to an immune response triggered by hepatitis C. These tests were not repeated during the current hospitalization, but are commonly associated with levamisole toxicity. ANA antibody, often a speckled pattern, and anti-ds DNA have been reported in cases of illness associated with cocaine and levamisole (12). In addition, patients who present with acute kidney failure have been shown to have pauci-immune focal necrotizing crescentic glomerulonephritis (12).

The most common skin biopsy findings in levamisole-induced vasculitis are leukocytoclastic vasculitis with perivascular lymphocytic infiltration, panniculitis, thrombotic microangiopathy, and necrosis. Patients classically present with hemorrhagic bullae, with or without necrosis. Notably, the cheeks and helixes are usually affected, along with the tip of the nose. Vasculitis may be the result of immune complex-mediated processes with vascular deposits of IgM, IgA, IgG, and C3. Retiform purpura—a reticular or netlike bruising—is often found in these patients.

The skin biopsy of our patient showed an ulcerated epidermis with pandermal neutrophilic infiltrate. However, no signs of small vessel thrombosis or vasculitis were present (Figure 1).

Test Methods

Several gas chromatographic methods have been developed for detection of levamisole in plasma with detection limits as low as 2 ng/mL in urine. The gas chromatography-mass spectrometry method provides a way to detect and measure levamisole in urine when unexplained agranulocytosis occurs, which is useful because patients are not likely to be aware of levamisole exposure. Because of the short half-lives of cocaine (0.8 ± 0.2 hours) and levamisole (5–6 hours), detection of these compounds in body fluids can be challenging. Liquid chromatography-tandem mass spectrometry can detect as little as 0.5 ng/mL of levamisole in urine up to three days after exposure (11). Our patient had levamisole at a concentration of 1.1 mcg/mL in the urine.

The treatment of cocaine/levamisole-induced vasculitis is immediate cessation of drug exposure and general supportive care. Our patient was treated with antibiotics and pain control medications. He was discharged to home with wound care instructions and close outpatient follow-up.

Conclusion

Over the past decade, levamisole has been identified as an adulterant in cocaine and reported to cause dangerous side effects in cocaine users. Patients who present with cutaneous manifestations of necrosis or vasculitis, immunologic evidence of autoantibodies, agranulocytocis, and cocaine abuse should be evalu-

ated for levamisole toxicity by urine analysis and skin biopsy to avoid unnecessary tests and delayed diagnosis. The correct diagnosis of levamisole-induced vasculitis prevents use of potentially dangerous other treatments, such as powerful immunosuppressive therapy.

Learning Objectives

After reading this article, the reader will be able to describe current trends in cocaine abuse, including adulterants, such as levamisole. The reader will also be able to describe the most serious complications and evaluate clinical testing results associated with cocaine/levamisole-induced toxicity.

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The authors have nothing to disclose.

α-Pyrrolidinovalerophenone

Dangerous New Cathinone Known As Flakka Evades Immunoassays

By Uttam Garg, PhD

In recent years, many new psychoactive substances of different chemical classes have emerged in the illicit drug market. Readily available from the Internet or street retailers at a relatively cheap price, these drugs are gaining in popularity because drug users like to experiment with new drugs. Drug users may also prefer new drugs because they are often undetected by the commonly used drug-screening systems. Most hospital labs use immunoassays that, for the most part, do not detect these new substances.

α-Pyrrolidinovalerophenone (α-PVP), also known as α-pyrrolidinopentiophenone, is one of these new designer drugs. It is closely related to pyrovalerone and methylenedioxypyrovalerone (MDPV) (Figure 1). α-PVP is the desmethyl analog of pyrovalerone and belongs to the cathinone class of stimulants, which are often referred to as "bath salts," "plant food," and "fertilizers." They are commonly labeled as "not for human consumption" or "for research use." α-PVP is sold under the street names "flakka" and "gravel." Flakka is the most common name; it is a colloquial Spanish term meaning pretty woman.

The drug was developed in the 1960s as a central nervous system (CNS) stimulant and pressor agent. It has emerged in the illicit drug market in the

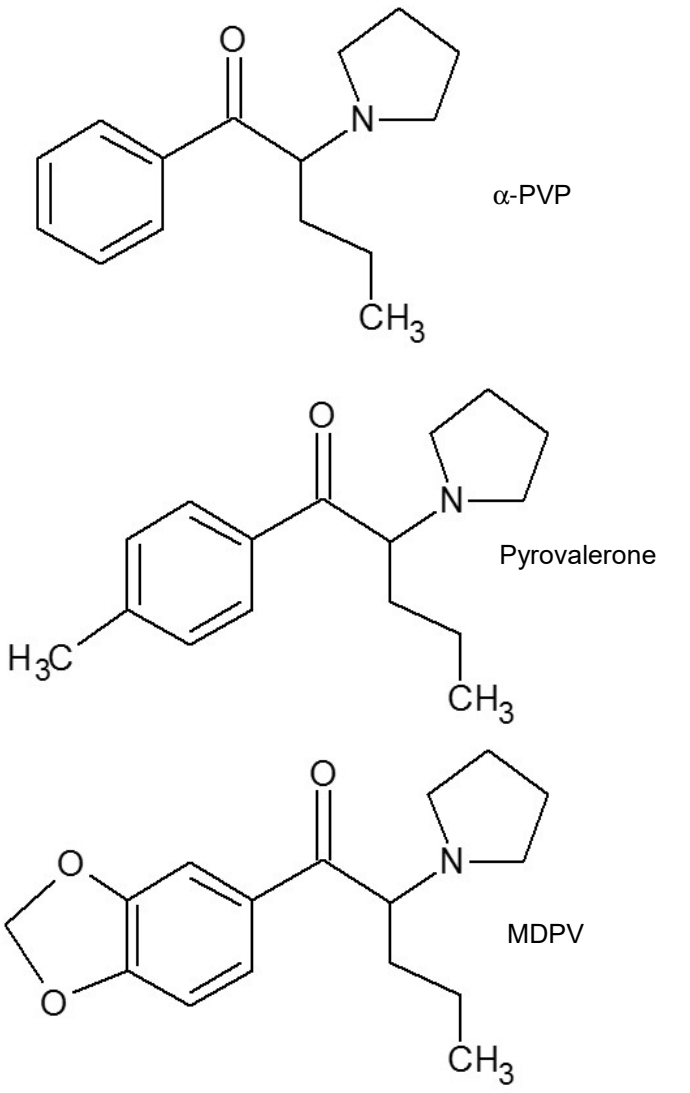

Figure 1. Chemical Structures of Selected Cathinones

past five years. Many countries, including the U.S., the United Kingdom, France, Germany, Finland, Australia, and Sweden, have passed regulations to temporarily or permanently ban many cathinones, including α-PVP. In the U.S., α-PVP is a schedule I controlled substance under the federal Controlled Substances Act.

Pharmacology and Metabolism

There is limited data on the pharmacology and metabolism of α-PVP. It is typically sold in powder or crystal forms, but liquid forms have been reported (Figure 2). Routes of administration include snorting, smoking, inhalation, intravenous injection, oral ingestion, and rectal insertion. Typical doses range from 50 to a few hundred milligrams. Because α-PVP is a psychostimulant, its actions at dopamine, norepinephrine, and serotonin transporters have been investigated in both in-vitro and in-vivo studies. Recent studies suggest that it inhibits dopamine and

Figure 2. α-PVP in Crystal Form
Source: https://www.drugabuse.gov/emerging-trends/flakka-alpha-pvp

norepinephrine uptake rather than stimulating their release (1–3).

Like other pyrovalerone cathinones, α-PVP is a CNS stimulant. Its immediate effects include enhanced energy, euphoria, empathy, openness, and increased libido. These effects may be followed by negative ones, such as tachycardia, increased blood pressure, agitation, confusion, hallucinations, seizures, and violent behavior (2–4). The effects begin 30–45 minutes after administration, peak at about 1.5 hours, and continue for three to eight hours (2).

There is limited data on α-PVP metabolism. In phase I metabolism, α-PVP undergoes reduction, hydroxylation, and pyrrolidine-ring-opening reactions. The reduced ketones give rise to 1-phenyl-2-(pyrrolidin-1-yl) pentan-1-ol (HO-PVP), which is the most abundant metabolite in human urine samples. At least seven phase I metabolites have been identified in urine. In phase II reactions, at least two glucuronide metabolites have been observed (1,5).

Laboratory Analysis

There is no commercial immunoassay for α-PVP. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) and gas chromatography-mass spectrometry (GC-MS) are the most commonly used assay methods. Several LC-MS/MS methods for the analysis of urine and blood have been described in the literature.

In one LC-MS/MS method, blood was diluted with 0.01 M carbonate buffer (pH 9.3) and spiked with an internal standard, α-PVP-d8. The mixture was vortexed and centrifuged. Drug was extracted using RP-18 solid-phase extraction cartridges. The eluate was dried and residue dissolved in a mixture of mobile phases. LC-MS/MS analysis involved a Poroshell 120 EC-C18 column, mobile phase A (water containing 0.2 % formic acid and 0.002 M of ammonium formate), mobile phase B (acetonitrile containing 0.2 % formic acid and 0.002 M of ammonium formate), and electrospray ionization in positive mode. Multiple

reaction monitoring transitions were m/z 232.1/91.1 (quantification) and 232.1/77.1 (qualification) for α-PVP; and m/z 240.3/91.1 and 240.3/77.1 for α-PVP-d8 (6). The assay measurement range was 0.01 to 0.50 mg/L.

Liquid chromatography–time-of-flight mass spectrometry and matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry methods have also been used (7,8).

GC-MS methods have also been published using alkaline liquid-liquid or solid-phase extraction procedures (9,10). In one of these, extraction of α-PVP along with other cathinones (methylone and ethylone) involved use of alkaline liquid-liquid extraction and n-butyl chloride (9). For sample cleanup, back-extraction involved acidification, separation, and waste of organic layer. Drugs from the aqueous phase were extracted by liquid-liquid alkaline extraction using chloroform. The extract was injected into the GC-MS for analysis. In this study, the presence of α-PVP was confirmed by LC-MS/MS.

Because α-PVP is prone to degradation at high temperatures, LC-MS/MS is the method of choice. Figure 3 shows a GC-MS spectrum of α-PVP.

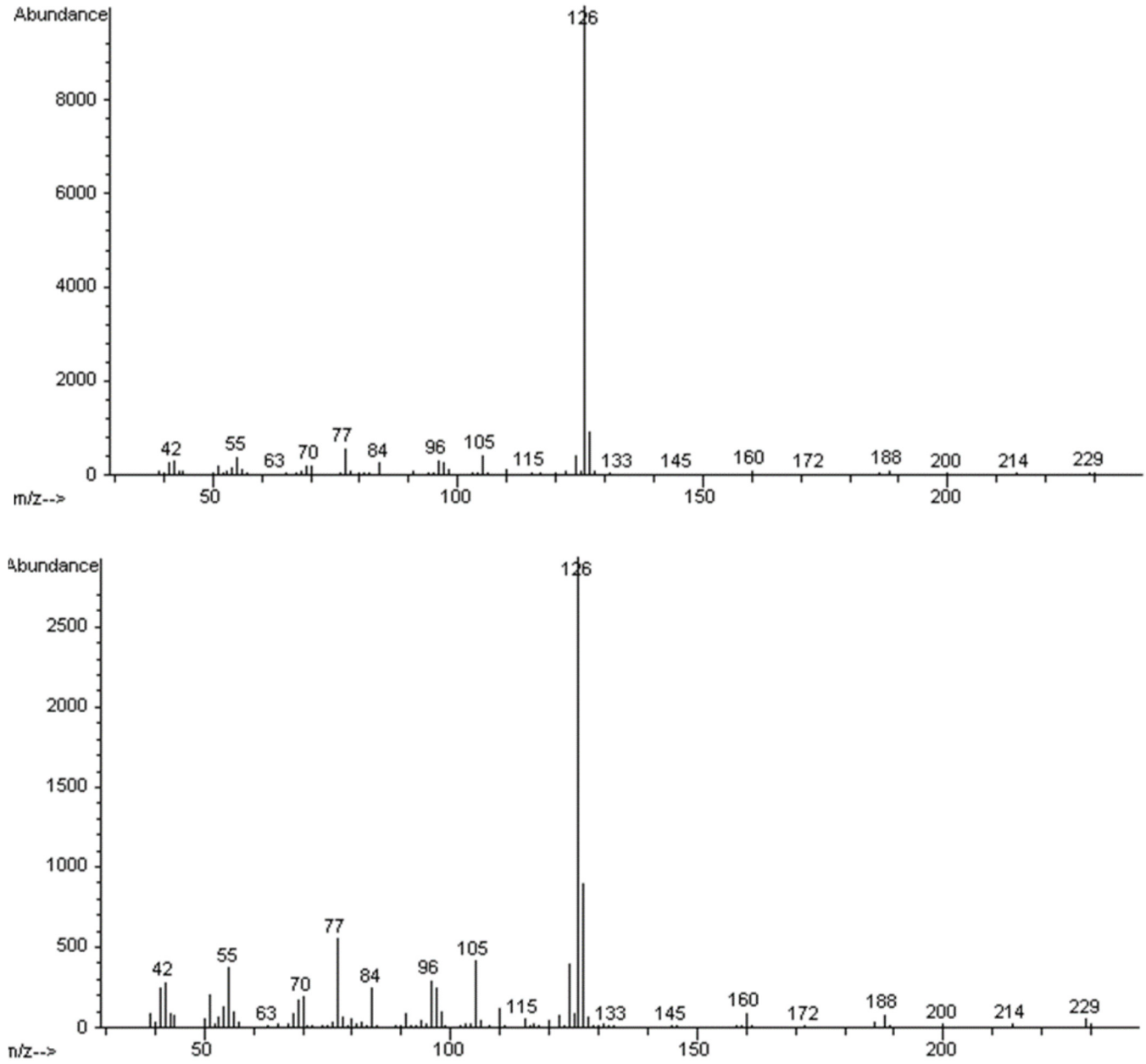

Figure 3. α-PVP GC-MS Spectrum. Two views of a gas chromatography-mass spectrometry α-PVP spectrum. The bottom figure is zoomed in four times.
Source: Scientific Working Group for the Analysis of Seized Drugs mass spectral library. www.swgdrug.org

Clinical Toxicity

Like other cathinones, such as MDPV, α-PVP is a powerful stimulant with high abuse potential. It can induce powerful effects, such as tachycardia, hypertension, agitation, violent behavior, and hallucinations. In the past five years, several hundred cases of intoxication, impaired driving, and death have been reported in the scientific literature or the media (2,4,11,12). A Google search of "drug news flakka" scored hits from a great many news outlets, including Fox News, CBS News, U.S. News, CNN, The Washington Post, and Rolling Stone.

Several scientific studies have examined cases of α-PVP use. In the U.S., the Virginia Department of Forensic Sciences reported 21 such cases (12). Eighteen cases of suspected impaired driving had an α-PVP blood concentration of <10–90 (median 30) ng/mL, with α-PVP alone detected in five of these 18 cases. The rest included other drugs, such as benzodiazepines, methamphetamines, and cannabinoids. Many of the impaired drivers exhibited CNS effects. It was difficult to determine whether the CNS effects were due to α-PVP or the combination of drugs. In three fatal cases, α-PVP blood concentrations were very high, ranging from 33–20,000 ng/mL.

Sweden's STRIDA project monitors the trends in new psychoactive substances as well as their clinical symptoms and toxicity. It reported 42 cases of α-PVP intoxication from 2012 to 2015 (4). The age range of these patients was 20 to 58 years, with males making up 79% of the cases. Of these 42 patients, two died. In the 40 nonfatal cases, major clinical manifestations included tachycardia (≥100 beats/minute), hypertension (systolic blood pressure ≥140 mm Hg), agitation, hallucinations, delirium, reduced consciousness, and mydriasis. Of the total cases, one-third involved only α-PVP, and two-thirds involved additional drugs. Serum α-PVP concentrations as measured by LC-MS/MS ranged from 4–606 (median 64) ng/mL. Urine concentrations ranged from 2–41,294 (median 1782) ng/mL.

In Japan, Umebachi et al. reported eight cases of α-PVP intoxication (3). The age range of these patients was 21 to 63 years, and six were male. Of note, three subjects took the drug in liquid form through rectal insertion. The patients exhibited psychiatric and neurological symptoms, tachycardia, hyperthermia, hypertension, lactic acidosis, and acid-base imbalance. Blood α-PVP concentrations in these patients ranged from 1–52 ng/mL.

Conclusion

α-PVP, commonly known as flakka, is a new cathinone that has appeared in the illegal drug market in the past five years. Epidemiology, pharmacology, and clinical data on α-PVP are limited. Its common effects include CNS stimulation, tachycardia, hypertension, and violent behavior. It can easily go undetected by routine drug-screening methods; LC-MS/MS and GC-MS are the preferred testing methods. There is no specific antidote, so treatment of α-PVP toxicity focuses on supportive and symptomatic care.

Learning Objectives

After reading this article, the reader should be able to describe the drug class of α-pyrrolidinovalerophenone (α-PVP); list and describe the laboratory methods for the analysis of α-PVP; and describe the clinical toxicity of α-PVP.

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AACC Webinar on Designer Drugs

"Designer Drugs: Keeping up from the Laboratory Perspective" is a webinar sponsored by the Society for Young Clinical Laboratorians and the AACC TDM-Toxicology Division to be held April 17.

The webinar will cover the three classes of designer drugs in common use (synthetic cannabinoids, cathinones, and fentanyl analogs), trends in designer drugs, and the testing challenges the drugs pose for clinical toxicology laboratories.

For information, visit: www.aacc.org/store/webinars/11200/designer-drug-testing-keeping-up-from-the-laboratory-perspective.

CAP Proficiency Testing Update

Two New Programs Begin in 2017

The College of American Pathologists is offering two new proficiency testing programs in 2017.

The Nicotine and Tobacco Alkaloids Survey will feature the analytes anabasine, cotinine, and nicotine. The survey consists of two shipments per year containing three 25.0-mL urine specimens.

The Pharmacogenetics Survey will feature the analytes dihydropyrimidine dehydrogenase, thiopurine methyltransferase, and UDP glucuronosyltransferase. It consists of two shipments per year containing three specimens of 25.0 micrograms of extracted DNA.

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